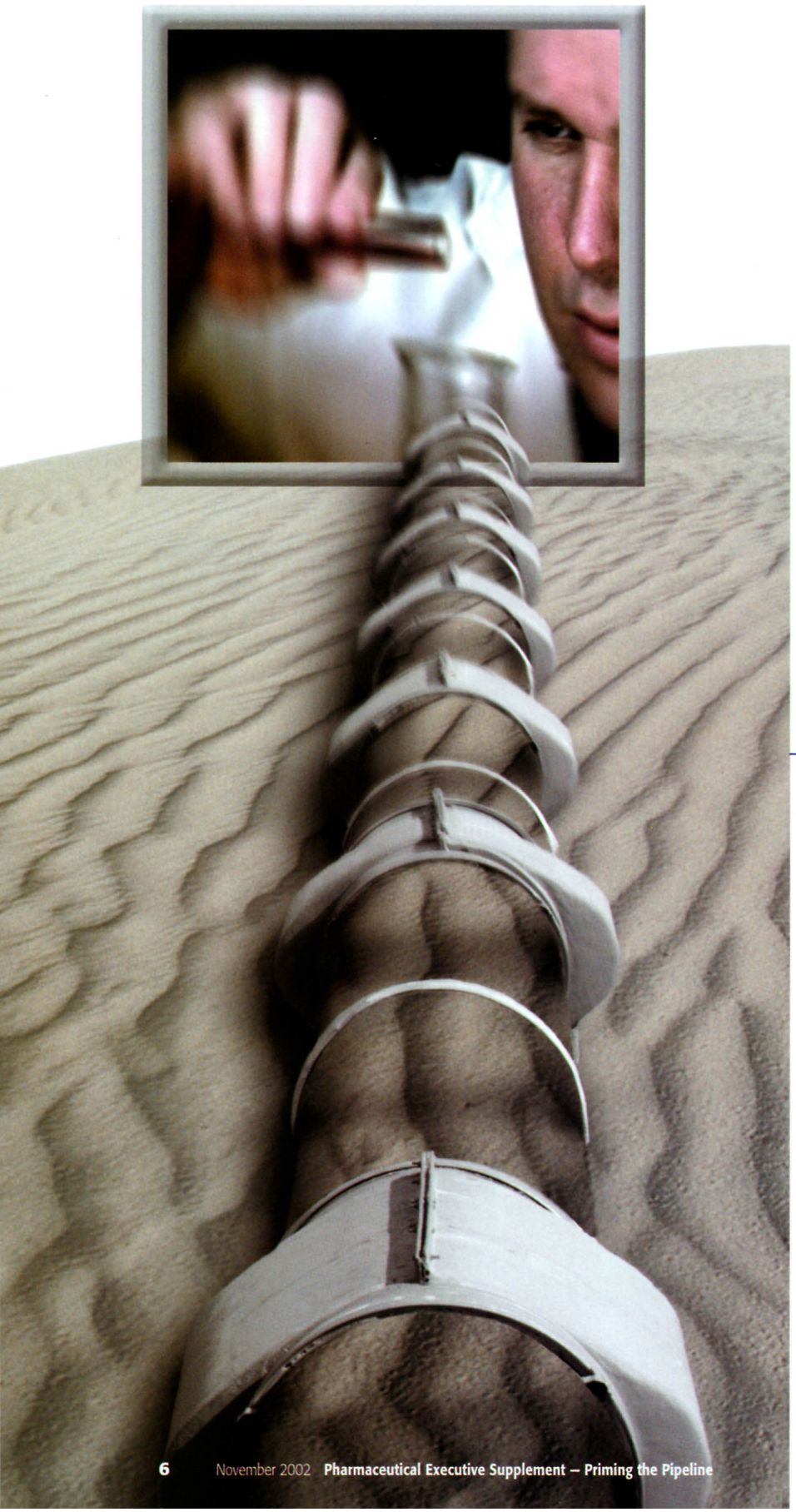

The Drug Drought

Primary Causes, Promising Solutions

Stan Bernard, MD, MBA

Pharma can alleviate its dry spell by leveraging new R&D technologies, marketing and digitizing clinical trials, and achieving "preferred partner" status.

It may be only temporary, but most industry indices reveal that pharma is experiencing a definite "drug drought." According to CMR International, in 2001 the rate of new products reaching global markets was the lowest in any ten-year period. Despite increasing investments in research and development—more than sevenfold within the past 20 years—to a record $30 billion in 2001, the number of new compounds approved in the United States remained

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fairly stable, at about 25 per year. To maintain the industry's historically high growth rate, pharma companies will have to introduce approximately three new products a year. But the current industry average is less than half that rate per company, resulting in an innovation gap that investors who are used to annual double-digit growth point to with dissatisfaction. According to Bernstein Research, the industry is unlikely to close that gap: Pharma R&D productivity has declined steadily since 1970, and it is expected to fall even further in the coming decade.

In short, the industry is failing to discover or source enough new compounds and to efficiently develop those it has. This article offers insight into the R&D causes of pharma's drought and suggests ways to alleviate it.

Why the Dry Spell?

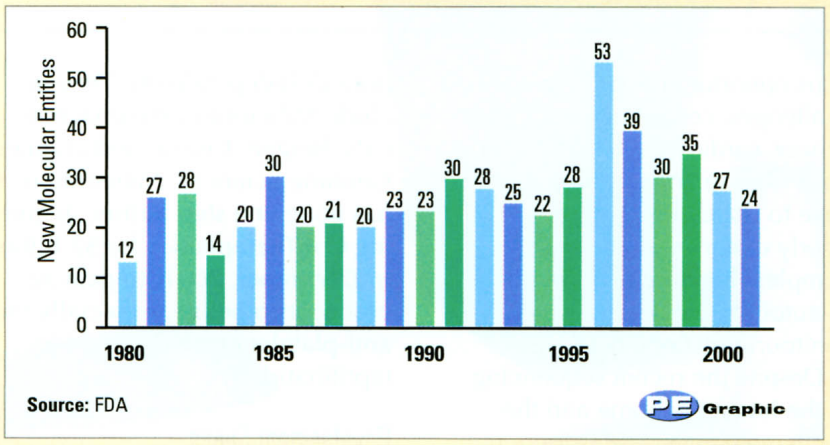
To understand the causes, it is important to separate R&D into its two distinct processes: 1) research, the process of discovering new compounds, and 2) development, the process of testing and preparing therapeutic candidates in clinical studies for regulatory approval. A company's performance is directly related to productivity in both research and development. The current drought results from deficiencies in both.

"We continue to face a confounding lag in research productivity," said Hank McKinnell, Pfizer's chairman and CEO, at a recent meeting of the Pharmaceutical Research and Manufacturer's Association. "Discovering new drugs is getting progressively more difficult and more expensive."

Discovery has become more difficult primarily because, since 1990, the industry has focused most of its research on four therapeutic areas that offered tremen-

FDA Approvals 1980–2001

The number of new compounds approved each year has essentially remained the same.

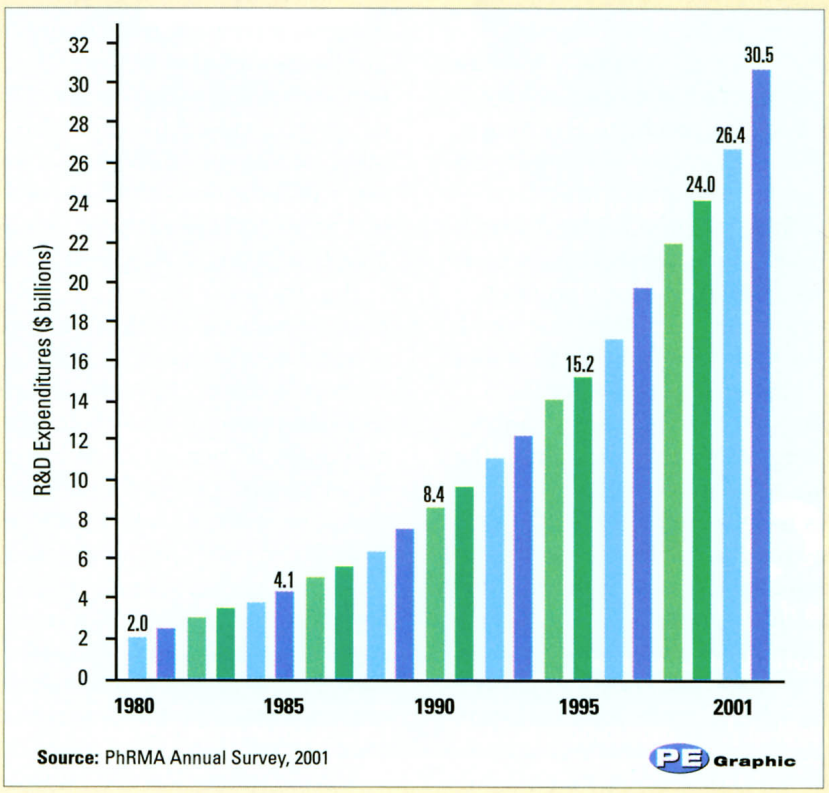


Source: FDA

PE Graphic

R&D Investment 1980–2001

The pharma industry has increased its R&D spending nearly sevenfold during the past two decades.



Source: PhRMA Annual Survey, 2001

PE Graphic

Being a "preferred partner" enhances Big Pharma's access to innovative compounds from smaller companies.

dous opportunities and innovation challenges: central nervous system, cancer, cardiovascular, and infectious disease. Increasingly, it will have to search for products in poorly understood and more complex therapeutic areas, such as autoimmune diseases and genitourinary conditions.

Despite the recent sequencing of the human genome and the excitement generated by genomic technologies, it's unlikely that those advances will significantly improve research productivity for a number of years. It has taken nearly two decades for biotechnology, first discovered in the 1970s, to have a significant impact on pharma's discovery process. But, according to a CMR International analysis, in the past five years, there has been a dramatic increase in the number of biotechnology-derived new products, reaching a high of 35 percent of all newly approved compounds in 2001.

A third factor reducing research productivity is the increasing competition to license new products. An extreme example of that trend is Bristol-Myers Squibb's $2 billion investment in ImClone for the rights to the experimental cancer treatment Erbitux (cetuximab). The tendency of major pharma companies to seek nearly 30 percent of new products from outside sources has intensified competition for innovative compounds.

To make matters worse, some of the smaller discovery companies with whom Big Pharma seeks to partner are now developing and commercializing their own compounds independently. They include Millennium Pharmaceuticals, Biogen, Celera, and Human Genome Sciences. Millennium has gone one step further, acquiring Cor Therapeutics for $2 billion in December, 2001, to gain access to its pipeline, especially the anti-platelet product Integrelin (eptifibatide).

Development Snags

Obstacles to product development intensify the industry's problems. According to data from Tufts University, the time needed for clinical development—exclusive of FDA approval times—has increased by 13 percent during the past two decades, adding nearly an extra year to the overall approval process. Increasing regulatory requirements are part of the problem. According to the online clinical trials company CenterWatch, it takes an average of 68 clinical trials, 4,000 patients, and 141 medical procedures per patient before a product gains FDA approval.

But regulators are not the only ones responsible for slowing down product development. Industry shares the blame. Its inefficiency in recruiting patients into clinical trials causes 90 percent of delays in development. CenterWatch reports that at least 80 percent of clinical trials fail to meet their enrollment deadlines, resulting in a cumulative daily loss of $1.3 million in sales for each therapeutic candidate. Patient retention in clinical trials is a closely related, albeit separate, challenge.

Second, pharma could improve its performance in identifying potential product toxicities before launch. Between 1997–2000, FDA recalled ten products because of safety concerns, including Johnson & Johnson's heartburn treatment Propulsid (cisapride), Warner-Lambert's diabetes agent Rezulin (troglitazone), and Bayer's lipid reducer Baycol (cerivastatin). At a cost of $1 billion to develop and commercialize the average therapy, recalls are costly and time consuming. They often result in increased patient morbidity, product liability lawsuits, tarnished corporate images, and soured relationships with patients, doctors, investors, and regulators.

Rainmaker Strategies

In pursuit of the discovery "advantage," large pharma companies have turned to the following:

"Preferred partner" status. By outsourcing the discovery process, they hope to increase the number of innovations—and spread the risk. Such partners offer new technologies, expertise, and capabilities, often at a lower cost and higher quality than those developed internally.

Several pharma companies have begun to implement an even more aggressive strategy for outsourcing that function. They seek "preferred pharma partner" status—to be the best in development, manufacturing, marketing, and sales for smaller companies with innovative compounds.

GlaxoSmithKline has emerged as a leading competitor in using the preferred partner strategy; it has in-licensed ten compounds within the last 12 months. Pfizer has gained "preferred" status by "insourcing." It partnered with Warner–Lambert and Pharmacia to co-market two blockbusters—Lipitor (atorvastatin) and Celebrex (celecoxib), respectively—and then acquired both

companies to control those products and others. Both companies chose Pfizer as a partner because of its marketing and sales prowess. With those acquisitions, Pfizer significantly augmented its already huge sales force, now totalling over 13,000 reps. That makes the company an even more attractive partner.

Link see **Partners** page 12

Clinical technologies. Companies may increasingly rely on licensing to identify new compounds, but they still need to ensure high internal rates of R&D productivity to hedge their product bets and to retain high product margins by avoiding licensing or royalty fees. Despite the time lags, to avoid future droughts pharma companies will have to invest in and leverage new R&D technologies, such as pharmacogenomics—using genomics to identify drug targets and to understand the impact of genetic variations on treatment response. By definition, pharmacogenomics has the potential to identify high quality therapeutic targets and decrease clinical trial sample sizes, resulting in faster, cheaper clinical trials.

Most pharmacogenomic and related genomic technologies are still years away from being able to shorten the R&D process. However, there are current examples of phamacogenomics applications helping bring products to market. Genentech's Herceptin (trastuzumab) is an anti-Her2 monoclonal antibody indicated for metastatic breast cancer treatment. Early in development, the drug showed poor efficacy in the vast majority of patients tested. That would typically halt development of a new product, but application of a pharmacogenomic test essentially rescued the therapy by identifying a niche market—the 25–30 percent of patients who would respond positively to it. In 1998, Herceptin was the first medicine ever approved by FDA in combination with a diagnostic test, the HercepTest. Worldwide sales of Herceptin now exceed $500 million.

Early industry reports suggest that pharmacogenomic technologies are helping not only to screen new compounds but also to expedite the identification of validated therapeutic targets. Opportunities exist to develop new treatments—or to rescue existing ones in danger of losing market share—in conjunction with diagnostic tests to identify early disease markers, niche markets within larger patient groups, or novel therapeutic uses.

Transformation of clinical trials. Companies that have re-engineered the clinical trials process have realized some incremental time and cost reductions. However, there are two major opportunities for pharma to dramatically change the product development process—marketing and digitizing clinical trials.

Ironically, pharma companies have not applied their marketing expertise to clinical trials, where they could generate tremendous cost and time savings. Marketing clinical trials takes many forms, but one of the most comprehensive approaches is the development and application of customer relationship management (CRM) strategies. With CRM, pharma companies can systematically profile investigators based on their experience, capabilities, and performance and match them with appropriate research. Companies should use marketing and CRM strategies more extensively to recruit, retain, and educate consumers about clinical trials.

The US Department of Defense and the National Health Service in the United Kingdom have demonstrated that involving patients in the development of trial protocols, drafting patient information materials, and serving on trial steering committees increase patient study recruitment and retention. In addition, clinical research teams should work more closely with marketers to take advantage of their marketing, media, and educational skills to recruit and retain patients in clinical studies.

The web and other digital technologies can enhance the effectiveness and speed of recruiting clinical trial investigators and patients, cutting the number of contacts and negotiations and the process from months to days. Most clinical trials still involve a cumbersome, paper-based process. (Less than 5 percent are web-based.) Researchers can digitize most studies' data and project management, resulting in less costly and time-consuming trials and significantly faster data collection, safety monitoring, data validation, and product approvals.

This, Too, Shall Pass

Pharma is experiencing an unusually dry spell of new product introductions, resulting primarily from a decline in R&D productivity because of difficult therapeutic targets, delays in the impact of new technologies, and increasing competition for sourcing innovative compounds. Inefficiencies in product screenings and clinical trial patient recruitment coupled with intensified regulatory requirements have reduced product development productivity.

To minimize the effects of the drought and to prevent future ones, companies must invest in promising new R&D technologies, enhance partnership capabilities, and leverage marketing and digital strategies in clinical trials. Fortunately for the industry, droughts are temporary and reversible aberrations. ▮